Predictors of Cerebral Infarction in Aneurysmal Subarachnoid Hemorrhage

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Background—Clinical and radiologic predictors of cerebral infarction occurrence and location after aneurysmal subarachnoid hemorrhage have been seldom studied.

Methods—We evaluated all patients admitted to our hospital with aneurysmal subarachnoid hemorrhage between 1998 and 2000. Cerebral infarction was defined as a new hypodensity located in a vascular distribution on computed tomography (CT) scan.

Results—Fifty-seven of 143 patients (40%) developed a cerebral infarction. On univariate analysis, occurrence of cerebral infarction was associated with a worse World Federation of Neurological Surgeons grade (P=0.01), use of ventriculostomy catheter (P=0.01), preoperative vasospasm (P=0.03), surgical clipping (P=0.02), symptomatic vasospasm (P<0.01), and vasospasm on transcranial Doppler ultrasonography (TCD) or repeat angiogram (P<0.01). On multivariable analysis, only presence of symptoms ascribed to vasospasm (P<0.01) and evidence of vasospasm on TCD or angiogram predicted cerebral infarction (P<0.01). TCD and angiogram agreed on the diagnosis of vasospasm in 73% of cases (95% CI, 63% to 81%), but the diagnostic accuracy of this combination of tests was suboptimal for the prediction of cerebral infarction occurrence (sensitivity, 0.72; specificity, 0.68; positive predictive value, 0.67; negative predictive value, 0.72). Location of the cerebral infarction on delayed CT was predicted by neurological symptoms in 74%, by aneurysm location in 77%, and by angiographic vasospasm in 67%.

Conclusions—Evidence of vasospasm on TCD and angiogram is predictive of cerebral infarction on CT scan but sensitivity and specificity are suboptimal. Cerebral infarction location cannot be predicted in one quarter to one third of patients by any of the studied clinical or radiological variables. (Stroke. 2004;35:1862-1866.)

Key Words: cerebral angiography ■ forecasting ■ stroke ■ subarachnoid hemorrhage ■ ultrasonography, transcranial, Doppler

Poorly understood and insufficiently treated, cerebral vasospasm remains one of the major threats to patients with aneurysmal subarachnoid hemorrhage (SAH).1,2 The reported incidence of brain infarction resulting from vasospasm varies according to the imaging technique used for diagnosis. Rates of cerebral infarction ranged between 24% and 35% in recent studies using computed tomography (CT) scan,3,4 but was much higher when relying on magnetic resonance imaging (MRI) to identify ischemic lesions, reaching up to 81% in one of the largest series.5

Brain ischemia may occur in patients without apparent vasospasm on transcranial Doppler ultrasonography (TCD) or angiogram. Conversely, documented vasospasm does not always portend neurological deterioration.6 Most studies assessing the diagnostic accuracy of TCD or angiogram used delayed neurological ischemic deficits (or symptomatic vasospasm) as the primary outcome measure. Much less is known about the value of these diagnostic tests to predict cerebral infarction on brain imaging.

Materials and Methods

We reviewed the clinical and radiological information of all patients admitted to the Mayo Clinic with acute aneurysmal SAH between January 1998 and December 2000, and the study was approved by our Institutional Review Board. Patients were included in the study if they had been admitted to our institution within 7 days of SAH onset and had a ruptured aneurysm documented by angiogram. Patients with fusiform, traumatic, and mycotic aneurysms were excluded. We reviewed 153 consecutive patients admitted during the study period. No patients who had denied access to their medical records for research purposes were included in the study. Ten patients were excluded from further analysis because they had declined to provide authorization to use their medical data for research purposes (3 patients), they had died before a follow-up CT scan could be obtained (4 patients), or had incomplete medical or radiological records (3 patients). Thus, the final study population consisted of 143 patients.
TCD recordings of the mean blood flow velocity (cm/sec) of the major anterior circulation vessels were measured through the trans-temporal window using a 2-MHz hand-held transducer probe. Studies were performed daily or every other day by 2 experienced technicians. Mean arterial velocities were ascribed to the vascular territory that could best explain deficits were ascribed to the vascular territory that could best explain deficits. Neurological deterioration (rebleeding, acute or worsening hydrocephalus, electrolyte disturbances, or hypoxia or seizures). Clinical deficits were classified as focal if the patient had new signs of neurological impairment but remained alert or only drowsy. All focal deficits were ascribed to the vascular territory that could best explain the symptoms. Global deficit was defined by the presence of stupor or coma (Glasgow coma scale sum score <10).

The primary outcome measure in our study was the occurrence of radiographic cerebral infarction. Secondary outcome measure was the functional status at the time of last follow-up using the modified Rankin scale (mRS) for assessment.

Statistical Analysis
We used the SAS software (SAS Institute Inc, SAS OnlineDoc Version 8). To evaluate whether there was a univariate association between cerebral infarction and quantitative risk factors, we used Wilcoxon rank sum tests. For categorical risk factors and cerebral infarction, we used chi-square tests.

We further evaluated predictors of cerebral infarction in a multi-variable setting using 2 distinct logistic regression models. In the first model, we specified a set of 7 independent variables in advance of any analyses. These variables were selected based on their presumed biological and clinical importance. The variables were sex, age, radiographic vasospasm by TCD or angiogram, Fisher grade, World Federation of Neurosurgery (WFNS) grade, SAH treatment, and aneurysm location. The number of variables chosen was limited by the number of cerebral infarction events. To expand on this analysis, we fit a second logistic regression model that included the 6 variables that were univariately associated with cerebral infarction (P<0.05).

We tested the sensitivity and specificity of TCD versus angiogram using the McNemar test among patients with cerebral infarction who received both radiographic measures and among the patients without cerebral infarction who were studied by both techniques. All statistical tests were 2-sided.

Results
The final analysis included 143 patients with acute aneurysmal SAH. Median age was 56 years (range 22 to 88 years) and 99 patients (69%) were women. Fifty percent of patients had history of smoking. After initial resuscitation, 112 patients (78%) were WFNS grade I to III. On admission CT scan, Fisher grade 3 was assigned to 76 patients (53%). The ruptured aneurysm was located in the anterior circulation in 107 patients (75%). Ninety-seven patients (68%) underwent surgical clipping, and 46 patients (32%) were treated with endovascular coil embolization. Median time to aneurysm treatment was 2 days (range 1 to 18 days). Every patient had at least 1 CT scan after surgery or endovascular treatment and at least one more CT scan after the diagnosis of vasospasm was made. Considering all the patients, mean time from SAH onset to last CT scan during acute hospitalization was 12 days (range 5 to 32 days). Twenty-three patients (16%) underwent endovascular treatment for vasospasm (angioplasty with or without intra-arterial papaverine in 11 patients and 12 intra-arterial papaverine only), with 8 patients requiring more than one treatment session. Only 1 case of cerebral infarction was attributed to a complication from endovascular treatment of vasospasm; this infarction was not included in the analysis.

Radiological cerebral infarctions occurred in 57 patients (40% of the study population). The distribution of demographic, clinical, and radiological characteristics according to cerebral infarction occurrence is shown in Table 1. On univariate analysis, clinical grade by WFNS (P=0.01), use of ventriculostomy catheter (P=0.01), preoperative vasospasm (P=0.03), surgical clipping (P=0.02), symptomatic vasospasm (P<0.01), and evidence of vasospasm by TCD or angiogram (P<0.01) were significantly associated with the occurrence of cerebral infarction. Using 2 different multiple
TABLE 1. Distribution of Demographic, Clinical, and Radiological Characteristics (Continuous Variables) According to Cerebral Infarction Occurrence in 143 Patients With Acute Aneurysmal SAH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cerebral Infarction</th>
<th>Cerebral Infarction</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population, n (%)</td>
<td>143</td>
<td>86 (60)</td>
<td>57 (40)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>143</td>
<td>56 y (22–87)</td>
<td>56 y (33–88)</td>
</tr>
<tr>
<td>Aneurysm size, median (range)</td>
<td>135</td>
<td>7 mm (2–25)</td>
<td>8 mm (3–26)</td>
</tr>
<tr>
<td>Time to treatment, median (range)</td>
<td>142</td>
<td>2 d (1–18)</td>
<td>2 d (1–14)</td>
</tr>
</tbody>
</table>

Variations and analysis considerations follow, as described in the text.
occurrence of cerebral infarction in approximately two thirds of cases. Similarly, cerebral infarction location was predicted more sensitively by the location of vasospasm on TCD. In fact, one third of the patients with brain infarction had no vasospasm documented by angiography in the vessel perfusing the area of ischemia. The presence of brain infarction on a CT scan correlated with increased mortality and worse functional outcome.

In this study, treatment modality (surgical clipping versus endovascular coiling) was not independently associated with the occurrence of cerebral infarction in multivariable analysis, despite a trend suggesting increased risk with surgical clipping. The confidence intervals were very wide, suggesting that significance may have been limited by a low patient number. In a larger study, we found surgical clipping to be associated with increased risk of stroke compared with endovascular coil embolization in patients with a good clinical grade. In the current series, the Fisher grade did not correlate with the occurrence of cerebral infarction in either univariate or multivariable analysis. A previous study has questioned the predictive value of the Fisher grade. Software-based techniques to quantify SAH on admission CT scan may be of greater value in predicting vasospasm.

Although focal symptomatic vasospasm may often be recognized by the development of localizing signs, the more common diffuse vasospasm may manifest more insidiously with a declining level of consciousness. As a consequence, defining symptomatic vasospasm is frequently challenging, both in research studies and at the bedside. For that reason, we chose brain infarction documented by CT scan as the main outcome measure of our study, as opposed to the more commonly used symptomatic vasospasm.

Studies using MRI have revealed that delayed ischemic lesions after SAH are usually bilateral and multifocal, often involve the frontal lobes, and are not uncommonly asymptomatic. It has been postulated that the lack of correlation of some of these lesions with angiographically-documented arterial narrowing may be because angiography does not have the sensitivity to visualize small-vessel spasm. Small-vessel spasm could also explain the dissociation between evidence of vasospasm by TCD or angiography and the presence of cognitive impairment after SAH. In fact, ischemic lesions, but not symptomatic vasospasm, have been found to be predictive of cognitive dysfunction in these patients.

Microembolism could be an alternative explanation for the occurrence of brain ischemic damage in the absence of vasospasm. Microembolic signals are frequently detected by TCD monitoring in patients with SAH with and without vasospasm; however, the clinical relevance of this finding remains to be established.

In general, TCD fares rather modestly in studies that used angiography as the “gold standard” for the definition of vasospasm. Meanwhile, when clinical deterioration was used to define vasospasm, TCD was found to be as sensitive as cerebral angiography. Against this background, our results offer new information that may enhance our understanding of the value of these 2 diagnostic techniques. We found that, in our experience, TCD was actually more sensitive but less specific than angiography in predicting the occurrence of cerebral infarction on CT scan. TCD and angiography disagreed in slightly more than 1 in 4 cases, and the combination of both tests still failed to provide high diagnostic accuracy.

In this study, the topography of the cerebral infarction on a CT scan was not predicted reliably by the location of documented vasospasm (by TCD or angiography), the location of the ruptured aneurysm, or the clinical manifestations of the patient. Therefore, cerebral ischemia was not frequently subclinical or clinically subtle, and it may have been caused by vasospasm that could not be detected by our standard diagnostic techniques.

We acknowledge that our study design has limitations. Although we tried to restrict our definition of cerebral infarction on a CT scan to focus on lesions likely caused by vasospasm, we cannot exclude that some of the ischemic lesions may have been caused by mechanisms other than vasospasm (eg, perforator vessel occlusion unnoticed at the time of surgical clipping or coil embolization, or delayed consequences of a dissection provoked during catheterization but undetected on an angiogram). Our definition of ultrasonographic vasospasm did not include measurement of the Lindegaard ratio; this measurement could have enhanced the specificity of TCD results by helping differentiate true vasospasm from hyperemia. Conversely, the diagnostic yield of angiography may have been limited by inappropriate timing or insufficient repetition of angiograms in patients who developed delayed ischemic damage. Also, it is conceivable that less conservative criteria for the definition of angiographic vasospasm could have enhanced the sensitivity of the test. Metallic artifacts from clips and coils used to secure the ruptured aneurysm may have interfered with the precise interpretation of findings in the CT scan, especially in the posterior fossa. Nevertheless, we consider that none of these potential limitations negates the validity of our results.

### TABLE 3. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of Vasospasm as a Diagnostic Predictor of Cerebral Infarction in 143 Patients With Acute Aneurysmal SAH

<table>
<thead>
<tr>
<th>N</th>
<th>Spasm</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV*</th>
<th>NPV†</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCD</td>
<td>120</td>
<td>0.90</td>
<td>0.44</td>
<td>0.55</td>
<td>0.86</td>
</tr>
<tr>
<td>Angiogram</td>
<td>113</td>
<td>0.75</td>
<td>0.63</td>
<td>0.60</td>
<td>0.77</td>
</tr>
<tr>
<td>Either TCD or angiogram</td>
<td>137</td>
<td>0.93</td>
<td>0.45</td>
<td>0.52</td>
<td>0.90</td>
</tr>
<tr>
<td>Both TCD and angiogram</td>
<td>96</td>
<td>0.72</td>
<td>0.68</td>
<td>0.67</td>
<td>0.72</td>
</tr>
</tbody>
</table>

*PPV indicates proportion of patients with vasospasm detected who had a cerebral infarction; NPV, proportion of patients with no vasospasm detected who did not have a cerebral infarction.
We conclude that evidence of vasospasm on TCD and angiogram is predictive of cerebral infarction on a CT scan. However, the sensitivity and specificity of these tests in predicting the occurrence of cerebral infarction are suboptimal.

References
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